

University of Groningen

Gender-specific risk factors for mortality associated with incident coronary heart disease - A prospective community-based study

van Jaarsveld, Cornelia H. M.; Ranchor, Adelita V.; Kempen, Gertrudis I. J. M.; Coyne, James C.; van Veldhuisen, Dirk J.; Ormel, Johan; Sanderman, Robbert

Published in:
Preventive Medicine

DOI:
[10.1016/j.ypmed.2006.06.010](https://doi.org/10.1016/j.ypmed.2006.06.010)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Jaarsveld, C. H. M., Ranchor, A. V., Kempen, G. I. J. M., Coyne, J. C., van Veldhuisen, D. J., Ormel, J., & Sanderman, R. (2006). Gender-specific risk factors for mortality associated with incident coronary heart disease - A prospective community-based study. *Preventive Medicine*, 43(5), 361-367. <https://doi.org/10.1016/j.ypmed.2006.06.010>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Gender-specific risk factors for mortality associated with incident coronary heart disease—A prospective community-based study

Cornelia H.M. van Jaarsveld^{a,*}, Adelita V. Ranchor^a, Gertrudis I.J.M. Kempen^b, James C. Coyne^c, Dirk J. van Veldhuisen^d, Johan Ormel^e, Robbert Sanderman^a

^a Northern Centre for Healthcare Research, Dept. of Public Health and Health Psychology, University Medical Centre Groningen, PO Box 196, 9700 AD Groningen, The Netherlands

^b Health Care Studies, Section of Medical Sociology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands
^c Behavioral Sciences University of Pennsylvania, Philadelphia, PA 19104, USA

^d Department of Cardiology, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands

^e Department of Social Psychiatry, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands

Available online 28 July 2006

Abstract

Background. Risk factors for mortality in community-residing persons developing congestive heart failure (CHF) and acute myocardial infarction (AMI) may differ for males and females.

Method. Persons from the Groningen Longitudinal Aging Study with incident CHF ($N=274$) or AMI ($N=198$) were identified between 1993 and 1998 and their survival status was collected in 2001. Risk factors are assessed prior to the cardiac diagnosis.

Results. The 1-, 5-, 7-year survival rates were 65, 53, 50% for AMI and 74, 45, 32% for CHF. Multivariate analyses showed that male gender, high age, smoking, diabetes and low physical function were risk factors for mortality among persons with CHF. For AMI, 1 month mortality was related to high age and baseline low body mass index, while longer term mortality was related to male gender and high age. In addition, diabetes increased longer term mortality among females but not among males with AMI. Depression was not a risk factor for mortality for either condition in either gender.

Conclusion. Males with CHF or AMI have worse survival rates compared to females. Risk factors for mortality are predominantly similar for males and females, except for diabetes which is a risk factor among females, but not males with AMI.

© 2006 Elsevier Inc. All rights reserved.

Keywords: Myocardial infarction; Congestive heart failure; Depression; Aged; Diabetes mellitus; Survival rate; Sex

Introduction

Coronary heart diseases (CHD), including acute myocardial infarction (AMI) and chronic heart failure (CHF), are associated with increased mortality (Goldberg et al., 1999; Levy et al., 2002). There are differences in the incidence and clinical presentations of CHD between males and females (Barrett-Connor, 1997; Chen et al., 1999; Van Jaarsveld et al., 2002). Better survival for female compared to male patients is reported (Kober et al., 1996; Levy et al., 2002). In AMI patients, contrasting results are found depending on whether short-term

(within 1 month) or longer term survival is studied. Increased mortality rates within 1 month after diagnosis is reported in young but not in older females (>65 years) (Abildstrom et al., 2003; Chen et al., 1999; Rosengren et al., 2001). Others report no gender difference (Galatius-Jensen et al., 1996) or increased short-term mortality among males (MacIntyre et al., 2001). Although results are contradictory, most studies among older persons indicate worse survival among males on the long term (Kober et al., 1996; Vaccarino et al., 2001).

The question remains what causes gender difference in mortality among CHD patients. One explanation concerns gender-related differences in the prevalence of risk factors for overall mortality such as smoking, body mass index and comorbidity (Yusuf et al., 2004). Second, risk factors may have differential effects for males and females. A meta-analysis

* Corresponding author. Fax: +31 50 3632406.

E-mail address: c.jaarsveld@ucl.ac.uk (C.H.M. van Jaarsveld).

showed that the impact of diabetes on CHD mortality is greater for females (Lee et al., 2000), while males show greater effects of disability, cholesterol and smoking (Janghorbani et al., 1993; Kattainen et al., 2004; Marang-van de Mheen et al., 2001).

Classic risk factors for mortality associated with CHD include gender, age, socio-economic status (Fried et al., 1998), marital status (Coyne et al., 2001), health status (e.g., hypertension and diabetes mellitus (Kannel and McGee, 1979; Sachdev et al., 2004), and potentially modifiable factors related to behavior (e.g., smoking and body mass index) (Fried et al., 1998). In addition, low self-rated health has been found to be a predictor for mortality (Idler and Benyamini, 1997). Although the mechanisms by which a self-rating of health predicts future mortality are diverse and largely unknown, ratings of self-rated health undoubtedly reflect inadequately measured and unmeasured objective factors, and it is suggested that the meaning of these self-ratings differ for males and females (Spiers et al., 2003). Depression has attracted particular attention because it is highly prevalent, a robust predictor for mortality in many populations, especially among AMI patients, and potentially modifiable by treatment (Barefoot et al., 1996; Frasure-Smith and Lesperance, 2003; Van Melle et al., 2004).

This study aims at identifying independent risk factors for mortality among community-residing persons who develop either CHF or AMI and determines whether effects of risk factors differ according to gender. Data originate from the Groningen Longitudinal Aging Study (GLAS) which offers an unusual opportunity, since it includes up to 8-year follow-up of persons with incident CHF and AMI. Moreover, data on risk factors are customarily collected after diagnosis. However, in the present paper, we present data on pre-morbid assessed risk factors.

Methods

Groningen longitudinal aging study

Detailed description of data collection is published elsewhere (Kempen et al., 1997a,b, 1998; Ormel et al., 1997). Briefly, the study population comprised 8723 persons aged 57 and older on January 1st 1993, who were registered as patients with the 27 general practitioners participating in the Morbidity Registration Network Groningen. 152 persons died or left the practice by the time contact was initiated. Useful baseline data were available for 5279 subjects (62%; 5279/(8723–152)).

Incident CHF or AMI

From 1993 until January 1st, 1998, all patients with a new post-baseline episode of AMI or diagnosis of CHF according to the criteria of the International Classification of Primary Care were identified by general practitioners (Lamberts and Wood, 1987). AMI was diagnosed if two of the following three symptoms were present: chest pain characteristic of myocardial ischemia lasting more than 15 min, abnormal ST-T changes or Q waves on an electrocardiogram, or elevation of blood cardiac enzymes. CHF was diagnosed if three of the following five symptoms were present: dependent edema, raised jugular venous pressure or hepatomegaly in the absence of liver disease, signs of pulmonary congestion or pleural effusion, enlarged heart, or dyspnoea in the absence of pulmonary disease.

During the enrolment period (1993–1998), 198 patients with a new episode of AMI and 274 patients with a first diagnosis of CHF after baseline were recruited. Cases with both diagnoses in the enrolment period ($N=28$) were included according to the first diagnosis. The study protocol was approved by the Medical Ethical Committee of the University Medical Centre Groningen.

Mortality

Survival was ascertained for all patients on June 1st 2001 using municipal registrations. All-cause mortality was included in this study. For several reasons, it is more relevant to study all cause mortality in a community-based older population as ours. Classification of causes of death always involves a subjective component (Gottlieb, 1997). Moreover, most older persons die as a consequence of a combination of factors, and the recorded cause of death may be less explanatory in older than in younger persons (Fried et al., 1998).

Risk factors for mortality

Risk factors are assessed during the baseline assessment in 1993, i.e., prior to the cardiac diagnosis.

Demographic risk factors include: gender, age, marital status (living with versus without a partner) and educational level (high versus low).

Baseline health status includes comorbidity, physical functioning, and self-rated health. Comorbidity is assessed with total number of 19 chronic medical conditions. In order to reduce report bias, only those conditions in the 12 months prior to the interview that required a GP or specialist consult and/or prescription of medicine were counted, which was found to be valid (Kriegsman et al., 1996). In addition the presence of hypertension and diabetes mellitus are analyzed separately.

Physical functioning was assessed with the Groningen Activity Restriction Scale (GARS), comprising 18 ADL (activities of daily living) and IADL (instrumental activities of daily living) items, each with four response categories. Scores may range from 18 (no physical dysfunction) to 72 (maximum level of physical dysfunction). Results of previous studies show that GARS meets the stochastic cumulative scalability criteria of the Mokken Model (Kempen et al., 1996; Kempen and Suurmeijer, 1990).

Self-rated health is assessed with a 1-item question: “how do you rate your overall health” (Miilunpalo et al., 1997). Scores were classified in two categories due to skewed distribution: 0 (excellent, very good, good), 1 (fair, bad).

Potentially modifiable risk factors include: smoking, Body Mass Index (BMI) and depression. Smoking behavior was assessed by a self-report questionnaire and defined in two classes: (0) never smoked cigarettes or cessation of smoking more than 10 years ago, and (1) current smoker or cessation of smoking less than 10 years ago. BMI was calculated as weight (kg) divided by the square of height (m^2) (both self-report), and categorized using cut-offs recommended by the World Health Organization: normal weight (18.5 to <25), overweight (25 to <30) and obese (≥ 30) (World Health Organization, 1998). Three underweight cases ($BMI < 18.5$) were excluded.

Depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS) (Spinhoven et al., 1997; Zigmond and Snaith, 1983). HADS has been validated for an older Dutch population (Spinhoven et al., 1997). Due to a skewed distribution, depression scores were dichotomized using a standardized cut point: 7 or lower (non-case) and 8 or higher (possible case) (Bjelland et al., 2002; Spinhoven et al., 1997; Zigmond and Snaith, 1983).

Analyses

Risk factors for mortality are analyzed for CHF using 8 year follow-up. In AMI patients, predictors for short-term mortality (within 1 month) and longer term mortality are analyzed separately. First, univariate hazards (odds ratios) associated with each risk factor were examined. Second, multivariate Cox proportional hazard analyses were performed with a stepwise forward conditional method including all potential risk factors. Finally, interaction (effect modification) between all risk factors and gender was tested with two-way product terms. Each interaction term (and the single risk factor, if not yet in the model) was successively added to the multivariate model to evaluate

Table 1

Baseline risk factors (prior to diagnosis) according to diagnosis and gender: the Groningen Longitudinal Aging Study, Groningen, The Netherlands, 1993–2001

	Persons with CHF			Persons with AMI		
	Males	Females	<i>p</i> ^a	Males	Females	<i>p</i> ^a
Number of patients (%)	131 (48)	143 (52)		122 (62)	76 (38)	
Age in years, mean (SD)	74.3 (7.1)	76.7 (7.7)	0.008	68.9 (7.9)	73.1 (7.6)	<0.001
Without partner (%)	21	64	<0.001	16	51	<0.001
Low educational level (%)	52	83	<0.001	49	82	<0.001
Smoking (%)	42	20	<0.001	48	34	0.050
BMI (%)						
Normal (18.5–<25)	45	39		39	54	
Overweight (25–<30)	49	43	0.011	52	35	0.067
Obese (≥30)	6	18		9	11	
Hypertension (%)	22	32	0.058	18	28	0.111
Diabetes (%)	9	18	0.029	10	15	0.322
Number of chronic conditions, mean (SD)	1.6 (1.4)	1.8 (1.5)	0.218	1.1 (1.0)	1.6 (1.4)	0.004
Physical disability, mean (SD)	24.9 (8.0)	30.0 (12.1)	<0.001	21.8 (5.6)	25.6 (8.3)	0.001
Depressive symptoms (≥8) (%)	26	37	0.048	17	22	0.370
Low self-rated health (%)	53	57	0.538	34	50	0.026

^a *P*-value of gender difference according to Chi-squared tests for categorical variables and *t*-tests for continuous variables.

possible interaction effects with gender. A *p* value of <0.05 was considered statistically significant. Analyses are performed with SPSS for windows version 12.

Results

Table 1 shows the prevalence of risk factors at baseline among males and females for both patient groups. Several risk factors are more pronounced among females, while smoking is more prevalent among male patients. Survival rates at several intervals are presented in Table 2.

Risk factors for mortality among persons with CHF

Table 3 shows the results of the Cox proportional hazard analyses among persons with CHF. At a univariate level, higher age, living without a partner, diabetes mellitus, high physical disability and low self-rated health are significantly related to mortality, but gender is not. Because several risk factors are more pronounced among females, while smoking is more prevalent among males, gender effects may be magnified or overlooked in univariate analyses. The multivariate model reveals five significant risk factors: male gender, higher age, smoking, diabetes mellitus and physical disability. This multivariate model shows that male gender is associated with a 1.7

increased mortality risk, after adjusting for the other four significant risk factors.

None of the two-way interaction terms of risk factors with gender is significant. However, additional multivariate analyses (not shown) indicated that smoking tended to be associated with a 1.9 significant increased risk among males (95% CI: 1.2, 3.0) but not among females (adjusted OR=1.2, 95% CI: 0.6, 2.2). Similarly, the multivariate adjusted risk associated with diabetes mellitus was 2.4 (95% CI: 1.4, 4.2) in females and non-significant among males (adjusted OR=1.6, 95% CI: 0.8, 3.0). Additional analyses on the other risk factors did not show such gender differential effects. However, the gender-specific effects of smoking and diabetes should be interpreted with caution, since the interaction terms were not significant (*P*=0.227 and *P*=0.324).

Risk factors for short-term and longer term mortality among persons with AMI

Table 4 shows the predictors for short-term (57 patients died within 1 month) and longer term mortality (37 died after 1 month) among persons with AMI. Again, gender is not related to mortality in univariate analyses. Multivariate analyses showed higher age and lower BMI to be related to short-term mortality. After adjustment for other risk factors, male gender is associated with a 3.2 increased mortality risk on longer term. In

Table 2

Survival rates at time intervals for persons with CHF or AMI: the Groningen Longitudinal Aging Study, Groningen, The Netherlands, 1993–2001

	Survival rates at time intervals in percent and [95% CI] ^a					
	1 month	6 month	1 year	2 years	5 years	7 years
CHF	90 [87, 93]	83 [79, 87]	74 [69, 79]	65 [59, 71]	45 [39, 51]	32 [25, 39]
AMI	71 [65, 77]	68 [62, 74]	65 [58, 72]	61 [54, 68]	53 [46, 60]	50 [42, 58]

^a Follow-up is complete up to 3 years; 5-year follow-up is available for 84% of persons with CHF and 82% of persons with AMI; 7-year follow-up is available for 66% of persons with CHF and 59% of persons with AMI.

Table 3
Predictors for mortality in persons with CHF, by Cox proportional hazard models: the Groningen Longitudinal Aging Study, Groningen, The Netherlands, 1993–2001

	Univariate		Multivariate	
	OR	[95% CI] ^a	OR _{adj}	[95% CI] ^a
Gender 0=female, 1=male	1.26	[0.93, 1.71]	1.68	[1.19, 2.37]**
Age per 10 years	1.72	[1.39, 2.14]***	1.96	[1.53, 2.50]***
Partner 0=with, 1=without	1.40	[1.03, 1.91]*		
Educational level 0=high, 1=low	1.09	[0.78, 1.53]		
Smoking 0=no, 1=yes	1.26	[0.91, 1.75]	1.60	[1.11, 2.31]*
BMI 0=normal, 1=overweight	1.02	[0.73, 1.42]		
0=normal, 1=obese	0.84	[0.50, 1.42]		
Hypertension 0=no, 1=yes	0.96	[0.68, 1.36]		
Diabetes Mellitus 0=no, 1=yes	1.58	[1.05, 2.37]*	1.98	[1.29, 3.03]**
Chronic conditions per 1 condition	1.03	[0.93, 1.14]		
Physical disability per 10 points	1.39	[1.23, 1.57]***	1.39	[1.20, 1.62]***
Depressive symptoms 0=non case, 1=possible case	1.02	[0.74, 1.42]		
Self-rated health 0=high, 1=low	1.46	[1.06, 2.00]*		

^a OR=odds ratio. CI=Confidence Interval of odds ratio. OR_{adj}=adjusted odds ratio for variables in the multivariate model.

* $P<0.05$.

** $P<0.01$.

*** $P<0.001$.

addition to male gender, higher age and diabetes mellitus predict longer term mortality. The interaction of gender and diabetes was borderline significant ($P<0.10$); diabetes mellitus tended to be a significant risk factor among females (adjusted OR=7.4, 95% CI: 2.0, 26.6) but not among males (adjusted OR=2.4, 95% CI: 0.9, 6.3).

Additional multivariate analyses, revealed male gender (OR=1.9, 95% CI: 1.1, 3.1), older age (OR=1.7 per decade, 95% CI: 1.3, 2.3), normal BMI (OR=0.5, 95% CI: 0.3, 0.8 for

overweight; OR=0.4, 95% CI: 0.1, 0.9 for obese), and diabetes among females (OR=2.8, 95% CI: 1.3, 6.2) as predictors for total (short- and longer term) mortality in persons with AMI (data not shown).

Gender-specific mortality rates

In Fig. 1, the survival functions belonging to the multivariate Cox models show the effects of gender. Male gender is

Table 4
Predictors for mortality in persons with AMI, by Cox proportional hazard models: the Groningen Longitudinal Aging Study, Groningen, The Netherlands, 1993–2001

	Short-term mortality (within 1 month)				Longer term mortality (after 1 month)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	[95% CI] ^a	OR _{adj}	[95% CI] ^a	OR	[95% CI] ^a	OR _{adj}	[95% CI] ^a
Gender 0=female, 1=male	0.80	[0.47, 1.33]			1.65	[0.80, 3.42]	3.19	[1.28, 7.94]*
Age per 10 years	1.78	[1.30, 2.44]***	1.57	[1.13, 2.18]**	2.06	[1.35, 3.14]**	2.33	[1.51, 3.60]***
Partner 0=with, 1=without	1.65	[0.97, 2.80]			1.06	[0.52, 2.20]		
Educational level 0=high, 1=low	1.09	[0.64, 1.87]			1.02	[0.52, 1.98]		
Smoking 0=no, 1=yes	0.96	[0.57, 1.63]			1.06	[0.55, 2.03]		
BMI 0=normal, 1=overweight	0.44	[0.25, 0.76]**	0.51	[0.29, 0.91]*	0.60	[0.29, 1.23]		
0=normal, 1=obese	0.00	[0.00, ∞] ^b	0.00	[0.00, ∞] ^b	0.73	[0.27, 2.02]		
Hypertension 0=no, 1=yes	1.18	[0.65, 2.16]			1.29	[0.61, 2.74]		
Diabetes Mellitus 0=no, 1=yes	1.07	[0.49, 2.37] ^c			3.18	[1.50, 6.75] ^{d,**}	♀7.37	[2.04, 26.6] ^{d,**}
Chronic conditions per 1 condition	1.05	[0.85, 1.30]			1.08	[0.83, 1.41]	♂2.35	[0.87, 6.31]
Physical disability per 10 points	1.10	[0.77, 1.56]			1.40	[0.90, 2.18]		
Depressive symptoms 0=non case, 1=possible case	0.88	[0.44, 1.73]			1.95	[0.96, 3.95]		
Self-rated health 0=high, 1=low	1.08	[0.63, 1.87]			1.27	[0.65, 2.50]		

^a OR=odds ratio. CI=Confidence Interval of odds ratio. OR_{adj}=adjusted odds ratio for variables in the multivariate model.

^b None of the 19 obese AMI patients died within 1 month.

^c Interaction term with gender is borderline significant ($P<0.10$): adjusted OR for diabetes in females=1.98 (95% CI: 0.78, 5.07) and in males OR=0.26 (95%CI: 0.04, 1.91).

^d Interaction term with gender is borderline significant ($P<0.10$), separate OR for males and females are presented for multivariate model.

* $P<0.05$.

** $P<0.001$.

*** $P<0.01$.

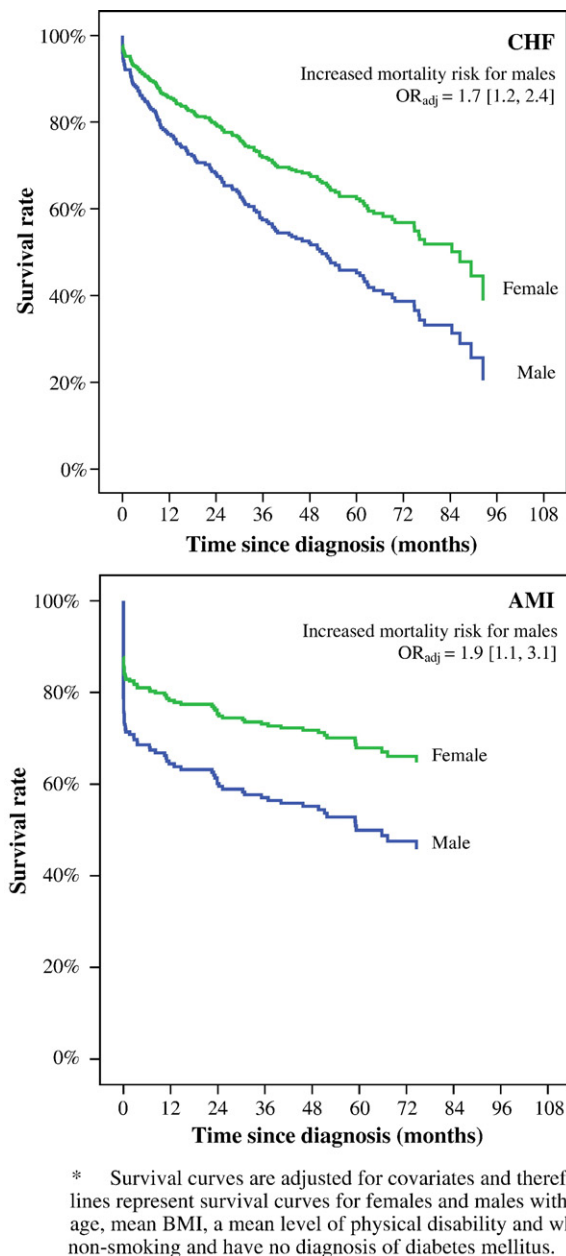


Fig. 1. Survival curves according to Cox models for patients with CHF and AMI (adjusted for covariates) by gender: the Groningen Longitudinal Aging Study, Groningen, The Netherlands, 1993–2001*.

associated with a 1.7 increased mortality risk in CHF and a 1.9 increased mortality risk in AMI (combining short-term and longer term mortality).

Discussion

One of the most striking findings was that in this sample, gender was a lurking variable (Joiner, 1981) predicting mortality for both CHF and AMI. Namely, in neither case did gender predict mortality in a simple univariate association; instead, being male emerged for both conditions as a

strong predictor of mortality only in multivariate analyses taking into account other classic risk factors.

We had postulated two broad strategies for explaining gender differences in mortality. The first focuses on differences in the prevalence of risk factors. We have demonstrated that the excess in mortality risk in males is not due to higher prevalence of other risk factors (such as smoking). In fact, most risk factors are more pronounced in females than in males.

The second explanation is that risk factors may have differential effects for males and females. Our results show indeed a differential effect of diabetes mellitus, which was a significant risk factor for longer term mortality among females with AMI but not among males with AMI. This gender-specific effect has been described earlier (Crowley et al., 2003; Lee et al., 2000), and suggested explanations include HDL cholesterol, estrogens, coagulation, patterns of obesity, or hyperinsulinemia (Lee et al., 2000) and lower use of effective cardiac medications in female than male diabetics (Crowley et al., 2003). The discussion of these theories and others is beyond the scope of this article; suffice to say that the underlying basis for the gender differences in risk from diabetes remains, for the most part, speculative. In addition, data suggest differential effect of smoking, which may be more relevant in male than in female patients. Gender differences in sensitivity to smoking has been reported, showing that males are more affected by smoking (i.e. higher mortality risks) than females (Marang-van de Mheen et al., 2001). Thus, risk factors for mortality showed few, albeit interesting, differences between males and females.

Mortality risk could thus be predicted by six characteristics: two demographic (high age and male gender), two health behavioral (low BMI and smoking), and two health parameters (diabetes mellitus and physical disability). In our elderly population, higher BMI was related to lower short-term mortality rates for AMI. These seemingly paradoxical finding might be seen in contrast with the literature on obesity as a robust risk factor for mortality (Fontaine et al., 2003). However, there is some consistency in findings that higher pre-existing BMI is actually associated with lower risk for mortality (Curtis et al., 2005; Eisenstein et al., 2005). In older age, a lower BMI might be a parameter of worse overall health, chronic disease like cancer, a disturbance of the metabolic system, worse eating habits or an indicator of physical infirmness. Another possible explanation relates to selective survivors, indicating that vulnerable overweighted people have died in earlier life and that the overweighted people in our older cohort represent a strong subgroup of overweight people. These indirect explanations are of particular interest since we found lower BMI to be a predictor of short-term mortality but not on longer term.

There is a large literature concerning mortality associated with depressive symptoms (Van Melle et al., 2004; Wulsin and Singal, 2003). Our results do not show any effect of depressive symptoms on mortality. One of the differences between our study with those finding an effect of depression is that depressive symptoms were assessed prior to diagnosis, not post-morbid. A post-morbid depression may be different from pre-morbid depression, and effects may differ with time (Barefoot et al., 1996).

Taken together, gender differences in the prevalence of risk factors and differential effects of these risk factors are relevant in examining the gender gap in mortality, but do not explain the increased mortality risk among male patients with CHD. Other factors thought to explain this gender gap include genetics, sex hormones, the pathophysiological origin and expression of CHF and AMI (Barrett-Connor, 1997). Furthermore, the gender gap may be related to differences in referral and therapeutic management (Bouma et al., 1999; Maynard et al., 1997). However, these differences all favor male patients and are therefore no help to explain the increased mortality rates for males. The increased mortality risk among males with CHD may also relate to overall worse survival among males in the general population. Females, who represent the majority of elder persons, have a higher life expectancy than males but they also experience a longer disabled life than males. The better survival of females has often been related to the protective role of estrogens (Isles et al., 1992). The role of estrogens has been related to cholesterol and also to the earlier discussed gender differential effect of diabetes, but may be less important in older (post-menopausal) women. Clearly, much interesting theories to explain the gender gap in mortality of CHD patients exist, and these theories are most definitely not mutually exclusive and research integrating several theories may be most relevant in explaining the gender gap.

Study strengths and limitations

In this study, risk factors were assessed prior to the cardiac diagnosis and this has several advantages, including that all incident cases in the cohort could be analyzed. This included also patients who died shortly after diagnosis and patients who would not give consent to participate in a study once they were diagnosed. These groups of patients are missed in studies that rely on data collection after diagnosis.

We demonstrated that the gender gap in mortality is not accounted for by other classic risk factors. Although we have included many risk factors, it can be that imbalances in the occurrence of other (unknown) risk factors related to gender are important.

Although our study included 472 patients with CHD, the power of our analyses may be limited since analyses are performed in subgroups according to the original diagnosis and included many different risk factors. Nevertheless, our results gain weight in presenting results for CHF and AMI separately, since identifying risk factors for specific diseases helps us understanding the pathways which originate the risks.

Conclusions

Mortality is increased among males with CHF or AMI, compared to female patients. Risk factors for mortality in newly diagnosed patients are predominantly similar for males and females, except for diabetes which is a risk factor among females but not among males. Female cardiac

patients with diabetes mellitus are a particularly high-risk group in need of targeted treatment strategies and enhanced lifestyle changes.

Acknowledgments

This research is part of the Groningen Longitudinal Aging Study (GLAS). GLAS is conducted by the Northern Centre for Healthcare Research and various Departments of the University of Groningen in The Netherlands. The primary departments involved are Public Health and Health Psychology, Family Medicine, Psychiatry, Sociology (ICS) and Human Movement Sciences. GLAS and its substudies are financially supported by the Dutch government (through NESTOR), the University of Groningen, the Faculty of Medical Sciences, the Dutch Cancer Foundation (NKB/KWF), and The Netherlands Organization for Scientific Research (NWO). Preparation of this paper was supported by grants from NWO, grant 904-59-104 and The Netherlands Heart Foundation (grant 2001-B084). The central office of GLAS is located at the Northern Centre for Healthcare Research, Groningen, The Netherlands (<http://www.med.rug.nl/nch/>). Prof. D.J. van Veldhuisen is an established investigator of The Netherlands Heart Foundation (grant D97-017).

References

- Abildstrom, S.Z., Rasmussen, S., Rosen, M., Madsen, M., 2003. Trends in incidence and case fatality rates of acute myocardial infarction in Denmark and Sweden. *Heart* 89, 507–511.
- Barefoot, J.C., Helms, M.J., Mark, D.B., Blumenthal, J.A., Califf, R.M., Haney, T.L., O'Connor, C.M., Siegler, I.C., Williams, R.B., 1996. Depression and long-term mortality risk in patients with coronary artery disease. *Am. J. Cardiol.* 78, 613–617.
- Barrett-Connor, E., 1997. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. *Circulation* 95, 252–264.
- Bjelland, I., Dahl, A.A., Haug, T.T., Neckelmann, D., 2002. The validity of the hospital anxiety and depression scale. An updated literature review. *J. Psychosom. Res.* 52, 69–77.
- Bouma, J., Broer, J., Bleeker, J., Van Sonderen, E., Meyboom-de Jong, B., DeJongste, M.J., 1999. Longer pre-hospital delay in acute myocardial infarction in women because of longer doctor decision time. *J. Epidemiol. Community Health* 53, 459–464.
- Chen, Y.T., Vaccarino, V., Williams, C.S., Butler, J., Berkman, L.F., Krumholz, H.M., 1999. Risk factors for heart failure in the elderly: a prospective community-based study. *Am. J. Med.* 106, 605–612.
- Coyne, J.C., Rohrbach, M.J., Shoham, V., Sonnega, J.S., Nicklas, J.M., Cranford, J.A., 2001. Prognostic importance of marital quality for survival of congestive heart failure. *Am. J. Cardiol.* 88, 526–529.
- Crowley, A., Menon, V., Lessard, D., Yarzebski, J., Jackson, E., Gore, J.M., Goldberg, R.J., 2003. Sex differences in survival after acute myocardial infarction in patients with diabetes mellitus (Worcester Heart Attack Study). *Am. Heart J.* 146, 824–831.
- Curtis, J.P., Selter, J.G., Wang, Y., Rathore, S.S., Jovin, I.S., Jadbabaie, F., Kosiborod, M., Portnay, E.L., Sokol, S.I., Bader, F., Krumholz, H.M., 2005. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch. Intern. Med.* 165, 55–61.
- Eisenstein, E.L., McGuire, D.K., Bhapkar, M.V., Kristinsson, A., Hochman, J.S., Kong, D.F., Califf, R.M., Van de, W.F., Yancy Jr., W.S., Newby, L.K., 2005. Elevated body mass index and intermediate-term clinical outcomes after acute coronary syndromes. *Am. J. Med.* 118, 981–990.

- Fontaine, K.R., Redden, D.T., Wang, C., Westfall, A.O., Allison, D.B., 2003. Years of life lost due to obesity. *JAMA* 289, 187–193.
- Frasere-Smith, N., Lesperance, F., 2003. Depression and other psychological risks following myocardial infarction. *Arch. Gen. Psychiatry* 60, 627–636.
- Fried, L.P., Kronmal, R.A., Newman, A.B., Bild, D.E., Mittelmarm, M.B., Polak, J.F., Robbins, J.A., Gardin, J.M., 1998. Risk factors for 5-year mortality in older adults: the cardiovascular health study. *JAMA* 279, 585–592.
- Galatius-Jensen, S., Launbjerg, J., Mortensen, L.S., Hansen, J.F., 1996. Sex related differences in short and long-term prognosis after acute myocardial infarction: 10 year follow up of 3073 patients in database of first Danish Verapamil Infarction Trial. *BMJ* 313, 137–140.
- Goldberg, R.J., Yarzebski, J., Lessard, D., Gore, J.M., 1999. A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective. *J. Am. Coll. Cardiol.* 33, 1533–1539.
- Gottlieb, S.S., 1997. Dead is dead—Artificial definitions are no substitute. *Lancet* 349, 662–663.
- Idler, E.L., Benyamini, Y., 1997. Self-rated health and mortality: a review of twenty-seven community studies. *J. Health Soc. Behav.* 38, 21–37.
- Isles, C.G., Hole, D.J., Hawthorne, V.M., Lever, A.F., 1992. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: comparison with men. *Lancet* 339, 702–706.
- Janghorbani, M., Hedley, A.J., Jones, R.B., Zhanpour, M., Gilmour, W.H., 1993. Gender differential in all-cause and cardiovascular disease mortality. *Int. J. Epidemiol.* 22, 1056–1063.
- Joiner, B.L., 1981. Lurking variables: some examples. *Am. Stat.* 35, 227–233.
- Kannel, W.B., McGee, D.L., 1979. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 241, 2035–2038.
- Kattainen, A., Reunanen, A., Koskinen, S., Martelin, T., Knekt, P., Aromaa, A., 2004. Disability predicted mortality in men but not women with coronary heart disease. *J. Clin. Epidemiol.* 57, 513–521.
- Kempen, G.I., Suurmeijer, T.P., 1990. The development of a hierarchical polytomous ADL-IADL scale for noninstitutionalized elders. *Gerontologist* 30, 497–502.
- Kempen, G.I., Miedema, I., Ormel, J., Molenaar, W., 1996. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. *Soc. Sci. Med.* 43, 1601–1610.
- Kempen, G.I., Jellic, M., Ormel, J., 1997a. Personality, chronic medical morbidity, and health-related quality of life among older persons. *Health Psychol.* 16, 539–546.
- Kempen, G.I., Ormel, J., Brilman, E.I., Relyveld, J., 1997b. Adaptive responses among Dutch elderly: the impact of eight chronic medical conditions on health-related quality of life. *Am. J. Public Health* 87, 38–44.
- Kempen, G.I., Miedema, I., Van den Bos, G.A., Ormel, J., 1998. Relationship of domain-specific measures of health to perceived overall health among older subjects. *J. Clin. Epidemiol.* 51, 11–18.
- Kober, L., Torp-Pedersen, C., Ottesen, M., Rasmussen, S., Lessing, M., Skagen, K., TRACE study group, 1996. Influence of gender on short- and long-term mortality after acute myocardial infarction. *Am. J. Cardiol.* 77, 1052–1056.
- Kriegsman, D.M., Penninx, B.W., Van Eijk, J.T., Boeke, A.J., Deeg, D.J., 1996. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J. Clin. Epidemiol.* 49, 1407–1417.
- Lamberts, H., Wood, M., 1987. *International Classification of Primary Care*. Oxford Univ. Press, Oxford.
- Lee, W.L., Cheung, A.M., Cape, D., Zinman, B., 2000. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 23, 962–968.
- Levy, D., Kenchaiah, S., Larson, M.G., Benjamin, E.J., Kupka, M.J., Ho, K.K., Murabito, J.M., Vasan, R.S., 2002. Long-term trends in the incidence of and survival with heart failure. *N. Engl. J. Med.* 347, 1397–1402.
- MacIntyre, K., Stewart, S., Capewell, S., Chalmers, J.W., Pell, J.P., Boyd, J., Finlayson, A., Redpath, A., Gilmour, H., McMurray, J.J., 2001. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J. Am. Coll. Cardiol.* 38, 729–735.
- Marang-van de Mheen, P.J., Smith, G.D., Hart, C.L., Hole, D.J., 2001. Are women more sensitive to smoking than men? Findings from the Renfrew and Paisley study. *Int. J. Epidemiol.* 30, 787–792.
- Maynard, C., Every, N.R., Martin, J.S., Kudenchuk, P.J., Weaver, W.D., 1997. Association of gender and survival in patients with acute myocardial infarction. *Arch. Intern. Med.* 157, 1379–1384.
- Miilunpalo, S., Vuori, I., Oja, P., Pasanen, M., Urponen, H., 1997. Self-rated health status as a health measure: the predictive value of self-reported health status on the use of physician services and on mortality in the working-age population. *J. Clin. Epidemiol.* 50, 517–528.
- Ormel, J., Kempen, G.I., Penninx, B.W., Brilman, E.I., Beekman, A.T., Van Sonderen, E., 1997. Chronic medical conditions and mental health in older people: disability and psychosocial resources mediate specific mental health effects. *Psychol. Med.* 27, 1065–1077.
- Rosengren, A., Spetz, C.L., Koster, M., Hammar, N., Alfredsson, L., Rosen, M., 2001. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. *Eur. Heart J.* 22, 314–322.
- Sachdev, M., Sun, J.L., Tsiatis, A.A., Nelson, C.L., Mark, D.B., Jollis, J.G., 2004. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. *J. Am. Coll. Cardiol.* 43, 576–582.
- Spies, N., Jagger, C., Clarke, M., Arthur, A., 2003. Are gender differences in the relationship between self-rated health and mortality enduring? Results from three birth cohorts in Melton Mowbray, United Kingdom. *Gerontologist* 43, 406–411.
- Spinoven, P., Ormel, J., Sloekers, P.P., Kempen, G.I., Speckens, A.E., Van Hemert, A.M., 1997. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol. Med.* 27, 363–370.
- Vaccarino, V., Krumholz, H.M., Yarzebski, J., Gore, J.M., Goldberg, R.J., 2001. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann. Intern. Med.* 134, 173–181.
- Van Jaarsveld, C.H.M., Sanderman, R., Ranchor, A.V., Ormel, J., Van Veldhuisen, D.J., Kempen, G.I.J.M., 2002. Gender-specific changes in quality of life following cardiovascular disease: a prospective study. *J. Clin. Epidemiol.* 55, 1105–1112.
- Van Melle, J.P., de Jonge, P., Spijkerman, T.A., Tijssen, J.G., Ormel, J., Van Veldhuisen, D.J., Van den Brink, R.H., Van den Berg, M.P., 2004. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom. Med.* 66, 814–822.
- World Health Organization, 1998. *Report of a WHO Consultation on Obesity. Obesity: Preventing and Managing the Global Epidemic*. World Health Organization, Geneva.
- Wulsin, L.R., Singal, B.M., 2003. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom. Med.* 65, 201–210.
- Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 364, 937–952.
- Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67, 361–370.